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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,455	08/09/2006	Norihiro Nishimoto	053466-0415	3174

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/575,455	NISHIMOTO ET AL.
	Examiner	Art Unit
	Lynn Bristol	1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/9/06; 8/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24 are all the pending claims for this application and all the claims under examination.

Information Disclosure Statement

2. The international and foreign patent references and the non-patent literature references cited in the IDS' of 8/9/06 and 8/23/07 have been considered and entered. Initialed 1449 sheets are attached hereto.

Specification

3. The specification is objected to failing to include the cross-reference to the priority documents, PCT/JP04/15674, filed 10/15/04, and Japan 2003-358152, filed 10/17/03.

Appropriate correction is required.

Claim Objections

4. Claims 2-12 and 14-24 are objected to for a grammatical error, where the phrase "wherein," should be replaced with ", wherein."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

5. Claims 9, 10, 12, 21, 22 and 24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if a hybridoma cell line which produces an antibody having the exact chemical identity of MR16-1 or PM-1 is known and publicly available, or can be reproducibly isolated without undue experimentation. The specification discloses the hybridoma clones for MR16-1 (p. 49, lines 22-24; FERM BP-5875) and PM-1 (p. 47, lines 29-32; FERM BP-2998) but does not include the date of deposit, the name and address of the depository and a statement of assurances that meet the conditions of the Budapest Treaty. The specification does not disclose amino acid or nucleotide sequence data for either clone that would enable a person of ordinary skill in the art to make a hybridoma cell line or an antibody produced therefrom having the same characteristics. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could

not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the hybridoma cell lines; (2) a hybridoma cell line which produces the chemically and functionally distinct antibodies claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. (FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)). Therefore, it would require undue experimentation to reproduce the claimed antibody species MR16-1 or PM-1. Deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made

under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit

and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Priority

6. The priority claim to the Japanese language foreign priority document, JP 2003-358152, filed 10/17/2003, is acknowledged as being filed upon national stage entry of this 371 application, however, Applicants' have not perfected their claim by providing a certified English-language translation of the document. Therefore the claims are accorded a priority date of 10/15/2004. Applicants are invited to submit a certified translation of the document or relevant portions thereof in their response to antedate any of the prior art rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Bielefeldt-Ohmann et al. (Can. Immunol. Immunother. 40:241-250 (1995); cited in the IDS of 8/9/06).

Claims 1 and 13 are interpreted as being drawn to an agent comprising an IL-6 antagonist with mesothelioma therapeutic properties (Claim 1) or an inhibitor comprising an IL-6 antagonist with mesothelioma growth inhibiting properties (Claim 13).

Bielefeldt-Ohmann discloses inhibiting mesothelioma cell growth with IL-6 antibodies because they produce IL-6 which is required for growth and an anti-IL-6 antibody can be used to inhibit malignant mesothelioma in vitro or in vivo in mice (Figure 3). The breadth of scope for the IL-6 antagonists of Claims 1 and 13 encompasses the IL-6 antibodies taught by the reference art, and therefore the claims are anticipated by Bielefeldt-Ohmann.

8. Claims 1 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Trikha (US 20040161426; published 8/19/04; priority to 2/4/03).

The interpretation of Claims 1 and 13 is discussed supra.

Trikha discloses IL-6 antagonists such as IL-6 antibodies [0018, 0019, 0022] that limit the growth, survival, and metastatic potential of tumor cells [0025] such as mesothelioma [0043]. The breadth of scope for the IL-6 antagonists of Claims 1 and 13 encompasses the IL-6 antibodies taught by the reference art, and therefore the claims are anticipated by Trikha.

9. Claims 1, 2, 4-6, 8, 9, 11, 12-14, 16-16-18, 20, 21, 23 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Lawless (US 20060094645; published 5/4/06; filed 10/6/04) as evidenced by Sato et al. (Can. Res. 53:851-856 (1993)).

The interpretation of Claims 1 and 13 is discussed supra.

Claims 2, 4-6, 8, 9, 11, 12 are interpreted as being drawn to an agent comprising an IL-6 antagonist with mesothelioma therapeutic properties where the mesothelioma is pleural mesothelioma (Claim 2), the IL-6 antagonist is an IL-6R antibody (Claim 4), the IL-6R antibody is a monoclonal (Claim 5), the monoclonal is to human IL-6R (Claim 6), the IL-6R antibody is recombinant (Claim 8), the human IL-6R antibody is PM-1 antibody (Claim 9), the IL-6R antibody is chimeric or humanized (Claim 11) and the humanized IL-6R antibody is humanized PM-1 (Claim 12).

Claims 14, 16-16-18, 20, 21, 23 and 24 are interpreted as being drawn to an inhibitor comprising an IL-6 antagonist with mesothelioma growth inhibiting properties

where the mesothelioma is pleural mesothelioma (Claim 14), the IL-6 antagonist is an IL-6R antibody (Claim 16), the IL-6R antibody is a monoclonal (Claim 17), the monoclonal is to human IL-6R (Claim 18), the IL-6R antibody is recombinant (Claim 19), the human IL-6R antibody is PM-1 antibody (Claim 20), the IL-6R antibody is chimeric or humanized (Claim 23) and the humanized IL-6R antibody is humanized PM-1 (Claim 24).

Lawless discloses pharmacological compositions comprising IL-6 antagonists [0067] for treating pleural mesothelioma [0049; 0055; 0107; 0111] where the antagonists comprise the IL-6 receptor antagonist, MRA [0064]. As evidenced by Sato, MRA is a humanized or reshaped antibody comprising the CDRs from the mouse anti-human IL-6R antibody from parent mouse PM-1 antibody and "is equivalent to both mouse and chimeric PM-1 antibodies in terms of antigen binding and growth inhibition" (p. 854, Col. 1, ¶2).

The claimed antibody appears to be the same as the prior art antibodies, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

10. Claims 1-4 and 13-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Carter et al. (US 20050090453; published 4/28/05; priority to 1/15/03).

The interpretation of Claims 1, 2 and 4 is discussed supra. Claim 3 is drawn to the agent where the pleural mesothelioma is malignant. The interpretation of Claims 13, 14 and 16 is discussed supra. Claim 15 is drawn to the inhibitor where the pleural mesothelioma is malignant.

Carter discloses IL-6 antagonists including glycoalkaloid compositions, agents that block the binding of IL-6 to its receptor [0050], small organic molecules, peptides, polypeptides and antibodies that bind to IL-6 or the receptor [0054], where the antagonists possess mesothelioma therapeutic effects [0071; 0103] by reducing the proliferation [0072] and reducing tumour cell aggressiveness, metastasis [0073]. The breadth of scope for the IL-6 antagonists of Claims 1 and 13 encompasses the small organic molecules, peptides, polypeptides and antibodies that bind to IL-6 or the receptor and the glycoalkaloid compositions taught by the reference art, and therefore the claims are anticipated by Carter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1, 4-12, 13 and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al. (US 20050090453; published 4/28/05; priority to 1/15/03) in view of Nishimoto et al. (Ann Rheum. Dis. 59(Suppl 1):i21-i27 (2000)).

The interpretation of Claims 1, 4-6, 8, 9, 11 and 12 and Claims 13, 16-18, 20, 21, 23 and 24 is discussed supra.

Claims 7 and 10 are interpreted as being drawn to an agent comprising an IL-6 antagonist antibody with mesothelioma therapeutic properties where the antibody is a monoclonal antibody against mouse IL-6R (Claim 7) and the antibody of Claim 7 is MR16-1 antibody (Claim 10).

Claims 19 and 22 are interpreted as being drawn to an inhibitor comprising an IL-6 antagonist antibody with mesothelioma growth inhibiting properties where the

antibody is a monoclonal antibody against mouse IL-6R (Claim 19) and the antibody of Claim 19 is MR16-1 antibody (Claim 22).

The claimed IL-6 antagonist therapeutic agent and IL-6 antagonist growth inhibitor agent were prima facie obvious at the time of the invention over Cater in view of Nishimoto.

The interpretation of Carter is discussed supra. Carter explicitly teaches using anti-IL-6 receptor antibodies having the properties of inhibiting mesothelioma growth but does not disclose human anti-IL-6R antibodies or the PM-1 antibody or mouse anti-IL-6R antibodies or the MR16-1 mouse antibody as does Nishimoto.

Nishimoto discloses blocking cytokine function using chimerised, humanized or fully human antibodies in treating cancers and targeting IL-6 which is a pleiotropic cytokine regulating oncogenesis (p. i21, Col. 1, ¶1). Nishimoto specifically discloses MR16-1 antibody (rat anti-mouse IL6R antibody (p. i23, Col. 1, ¶2)) in regulating the immunoregulatory effects of IL-6 as well as the MRA antibody, the humanized anti-human IL6R antibody derived from the mouse anti-human IL-6R antibody, PM-1 (p. i23, Col. 2, ¶2; p. i24, Col. 2, ¶3).

One skilled in the art would have been motivated to have produced and would have been reasonably assured of success in having produced the -6 antagonist therapeutic agent and IL-6 antagonist growth inhibitor agent each comprising human and mouse monoclonals directed against IL6R based on the combined disclosures of Carter and Nishimoto. Each of Carter and Nishimoto explicitly teach the use of IL-6R antibodies having therapeutic or growth inhibiting effects for cancers, and Carter

specifically teaches that mesothelioma is readily targetable for antibody therapy. Each of Carter and Nishimoto disclose anti-IL-6R antibodies and Nishimoto discloses that humanizing the antibodies has the advantages of producing less immunogenicity (p. i24, Col. 2, ¶3). Nishimoto discloses that MR16-1, PM-1 and MRA antibodies can used to inhibit tumor cell growth. One skilled in the art would found more than sufficient motivation to have combined the MR16-1, PM-1 and MRA antibodies of Nishimoto with the IL-6 antagonists of Carter, because the the MR16-1, PM-1 and MRA antibodies of Nishimoto were antagonistic for IL-6 by binding to the IL-6R. One skilled in the art would have been reasonably assured of success in having produced the IL-6 antagonist therapeutic agent and IL-6 antagonist growth inhibitor agent based on Carter and Nishimoto because each of the references taught IL-6 antagonists comprising IL-6R antibodies could be used in cancer therapeutics given the pleiotropism of IL-6 for cancers more especially mesothelioma based on Carter. The claimed IL-6 antagonist therapeutic agent and IL-6 antagonist growth inhibitor agent were prima facie obvious over Carter and Nishimoto for the foregoing.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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